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DOI:

[10.1111/bjd.17590](https://doi.org/10.1111/bjd.17590)

*Document Version*

Peer reviewed version

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*Citation for published version (APA):*

van Zuuren, E. J., Fedorowicz, Z., Tan, J., van der Linden, M., Arents, B., Carter, B., & Charland, L. (2018). Interventions for rosacea based on the phenotype approach: An updated systematic review including GRADE assessments: Evidence based treatments for rosacea based on phenotype approach. *British Journal of Dermatology*. <https://doi.org/10.1111/bjd.17590>

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## **Interventions for rosacea based on the phenotype approach: An updated systematic review including GRADE assessments**

Esther J van Zuuren<sup>1</sup>, Zbys Fedorowicz<sup>2</sup>, Jerry Tan<sup>3</sup>, Mireille MD van der Linden<sup>4</sup>, Bernd WM Arents<sup>5</sup>, Ben Carter<sup>6</sup>, Lyn Charland<sup>7</sup>

<sup>1</sup>Dermatology Department, Leiden University Medical Centre, Leiden, 2333 ZA, the Netherlands

<sup>2</sup>DynaMed Plus, EBSCO Health, 10 Estes Street, Ipswich, MA 01938, United States

<sup>3</sup>Department of Medicine, University of Western Ontario, London, Canada

<sup>4</sup>Department of Dermatology, Amsterdam University Medical Centres, Amsterdam, Netherlands

<sup>5</sup>Skin Patients Netherlands (Huidpatiënten Nederland), Nieuwegein, the Netherlands

<sup>6</sup>Biostatistics and Health Informatics, King's College London; Institute of Psychiatry, Psychology & Neuroscience, London, UK

<sup>7</sup>Independent researcher and consumer referee, Quebec, Canada

Corresponding author: Esther J van Zuuren

Department of Dermatology B1-Q

Leiden University Medical Centre

PO Box 9600, 2300 RC Leiden, the Netherlands

Tel: +31715262497

Fax: +31715248106

e-mail: e.j.van\_zuuren@lumc.nl

Running head: Evidence based treatments for rosacea based on phenotype approach

Funding sources: Dutch Society of Dermatology and Venereology

Conflict of interest: Zbys Fedorowicz, Ben Carter, Bernd Arents and Lyn Charland have no declarations of interest.

Esther van Zuuren serves on the global rosacea consensus panel (ROSCO) and received non-financial support and other from Galderma in October 2016.

Jerry Tan has been an advisor, consultant, investigator and/or speaker for Allergan, Bayer, Cipher, Galderma and Valeant. He was a co-author of the Canadian Rosacea Clinical Practice Guidelines and is the co-chair of the global rosacea consensus panel (ROSCO) and serves on the expert panel of the National Rosacea Society (NRS). He was an investigator in the following trials: Stein L, Kircik L, Fowler J *et al.* Efficacy and safety of ivermectin 1% cream in treatment of papulopustular rosacea: results of two randomized, double-blind, vehicle-controlled pivotal studies. *J Drug Dermatol* 2014; **13**:316-23; Stein Gold L, Kircik L, Fowler J, *et al.* Long-term safety of ivermectin 1% cream vs azelaic acid 15% gel in treating inflammatory lesions of rosacea: results of two 40-week controlled, investigator-blinded trials. *J Drug Dermatol* 2014; **13**:1380-6; Stein-Gold L, Papp K, Lynde C *et al.* Treatment of Rosacea With Concomitant Use of Topical Ivermectin 1% Cream and Brimonidine 0.33% Gel: A Randomized, Vehicle-controlled Study. *J Drug Dermatol* 2017; **16**:909-16; Tan JKL, Girard C, Krol A *et al.*

Randomized placebo-controlled trial of metronidazole 1% cream with sunscreen SPF 15 in treatment of rosacea. *J Cutan Med Surg* 2002; **6**:529-34.

Mireille van der Linden received non-financial support and other from Galderma in October 2016, she received speaker fees from Janssen Cilag and Abbvie. Furthermore, she was an investigator in the following trial: van der Linden MMD, van Ratingen AR, van Rappard DC *et al.* DOMINO, doxycycline 40 mg vs. minocycline 100 mg in the treatment of rosacea: a randomized, single-blinded, noninferiority trial, comparing efficacy and safety. *Br J Dermatol* 2017; **176**:1465-74.

Word count abstract: 249

Word count text: 5752

Number of tables: 1

Number of figures: 2

Number of Supplementary files: 1

What is already known about this topic?

- Rosacea is a chronic facial inflammatory dermatosis
- The diagnosis and classification of rosacea have evolved from a subtype to a phenotype approach
- Effective and safe interventions include brimonidine in temporarily reducing persistent erythema; laser and light based therapies for mainly telangiectasia; topical azelaic acid, metronidazole and ivermectin, along with oral doxycycline and isotretinoin for papules/pustules; and topical ciclosporin ophthalmic emulsion for ocular rosacea

What does this study add?

- Phenotype-based approach with GRADE certainty of evidence assessments
- Topical oxymetazoline reduces temporarily persistent erythema (moderate certainty evidence)
- There is moderate certainty of evidence that topical minocycline is effective in treating papules/pustules, and oral minocycline is as effective as doxycycline 40 mg
- Low dose isotretinoin 0.25 mg/kg greatly reduces papules/pustules compared to placebo (high certainty evidence)
- Omega-3 fatty acids improve symptoms of dry eyes and tear gland function (moderate certainty evidence)

## ABSTRACT

### Background

Rosacea is a common chronic facial dermatosis. Classification of rosacea has evolved from subtyping to phenotyping.

### Objectives

Updating our systematic review on interventions for rosacea.

### Methods

We searched: CENTRAL in *The Cochrane Library*, MEDLINE, EMBASE, LILACS, Science Citation Index, and ongoing trials registers (March 2018) for randomised controlled trials. Study selection, data extraction, risk of bias assessment and analyses were carried out independently by two authors. GRADE was used to assess certainty of evidence.

### Results

We included 152 studies (46 were new), comprising 20,944 participants. Topical interventions included: brimonidine, oxymetazoline, metronidazole, azelaic acid, ivermectin and other topical treatments. Systemic interventions included: oral antibiotics, combinations with topical treatments or other systemic treatments. Several studies evaluated laser or light-based treatment.

We present the most current evidence for rosacea management based on a phenotype-led approach.

### Conclusions

For reducing temporarily persistent erythema: there was high certainty evidence for topical brimonidine and moderate certainty for topical oxymetazoline; for erythema and mainly telangiectasia: low to moderate certainty evidence for laser and intense pulsed light therapy.

For reducing papules/pustules: there was high certainty evidence for topical azelaic acid and topical ivermectin; moderate to high certainty evidence for doxycycline and isotretinoin; moderate certainty evidence for topical metronidazole, and topical minocycline and oral minocycline being equally effective as doxycycline 40 mg. There was low certainty evidence for tetracycline and low dose minocycline.

For ocular rosacea, there was moderate certainty evidence that oral omega-3 fatty acids were effective and low certainty evidence for ciclosporin ophthalmic emulsion and doxycycline.

## INTRODUCTION

Rosacea is a chronic inflammatory dermatosis affecting the cheeks, nose, eyes, chin and forehead. It is characterised by recurrent episodes of flushing or transient erythema, persistent erythema, papules, pustules, and telangiectasia.<sup>1-4</sup> In 2002, the National Rosacea Society Expert Committee (NRSEC) of the United States proposed standardised criteria for diagnosis and classification of rosacea.<sup>5</sup> They posited that any one of the following primary features in a centrofacial distribution sufficed for diagnosis: flushing, non-transient erythema, papules/pustules or telangiectasia. Secondary features included burning/stinging, erythematous plaques, dry appearance, oedema, peripheral location, phymatous changes and ocular manifestations. Furthermore, they grouped some of these features into four subtypes and one variant: erythematotelangiectatic, papulopustular, phymatous, ocular and granulomatous rosacea (the variant).<sup>5</sup>

However, shortcomings in these diagnostic criteria and subtyping have become apparent.<sup>6</sup> This includes the lack of specificity of some primary features (flushing, papules/pustules, telangiectasia), the exclusion of phyma as a primary feature, and the conflation of multiple features into subtypes.<sup>6</sup> For example, the erythematotelangiectatic subtype comprises flushing and persistent central facial erythema with, or without telangiectasia while the papulopustular subtype comprises persistent central facial erythema with transient, central facial papules and/or pustules. Thus, both have persistent central facial erythema as a common feature. This has led to confusion in epidemiological research whereby some studies consider them as separate categories while others aggregate all with central facial erythema as erythematotelangiectatic, a subgroup of which is papulopustular. Furthermore, it does not account for patients presenting with a solitary diagnostic criterion and absence of the others defining a specific subtype. For example, how would one classify a patient with persistent central facial erythema alone but without flushing and telangiectasia? In addition, severity determination of subtypes is complicated by the presence of multiple features each of which may vary in individual severity and responsivity to intervention. However, these individual features were not previously typically evaluated separately. Furthermore, in clinical practice, subtyping may inadequately capture the signs and symptoms of individual patients as some features can extend across subtypes.

Consequently, revised diagnostic criteria have been proposed and recommendations made to abandon the subtyping approach. Both an international Rosacea Consensus panel and updated NRSEC guidance have recommended harmonized diagnostic criteria and a phenotype-led approach.<sup>6,7</sup> The following features represent independent diagnostic criteria of rosacea: fixed centrofacial erythema that may periodically intensify, or phymatous changes. In their absence, diagnosis can also be established by two or more major features: papules/pustules, flushing,

telangiectasia, ocular manifestations (lid margin telangiectasia, interpalpebral conjunctival injection, spade shaped infiltrates in the cornea, scleritis and sclerokeratitis).<sup>7</sup> While secondary features may occur - burning or stinging, oedema, dry appearance – these are not generally considered diagnostic, either alone or in combination. This redirection in diagnosis and elimination of subtypes should provide greater accuracy in diagnosis, establish clearly defined targets for research, facilitate development of severity measures and improve patient-centred care.<sup>7</sup>

Management strategies for people with rosacea should include phenotype-based treatments, in accordance with current classification of rosacea (instead of the previous subtype-classification).<sup>7,8</sup> As rosacea can have an adverse impact on quality of life, these strategies should also be directed towards achieving improvements in general well-being by targeting those aspects most bothersome to the patient.<sup>1,8,9</sup>

The objectives of this systematic review were to examine the different management options and to determine the most effective strategies in the treatment of rosacea. Furthermore, this review more closely aligns evidence-based treatment options with the new phenotype approach.

As the Cochrane Skin Group recently decided to facilitate the regular update of only a few systematic reviews, this update of the Cochrane review is published in the British Journal of Dermatology. The content of the full updated review is provided in Supplementary file 1.

## **MATERIAL AND METHODS**

This updated systematic review conforms to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement<sup>10</sup> and followed a prespecified protocol.<sup>11</sup>

### **Inclusion criteria**

Randomised controlled trials (RCTs) examining all types of interventions in people with rosacea.

### **Outcome measures**

Our primary outcomes were: quality of life, participant-assessed rosacea severity and proportion of participants reporting an adverse event. Secondary outcome measures were physician-assessed rosacea severity, assessment of erythema and telangiectasia, lesion counts, time to improvement and duration of remission.

### **Search strategies**

We searched several databases to 6 March 2018: CENTRAL in *The Cochrane Library*, MEDLINE, EMBASE, LILACS, and Science Citation Index, for the search strategies see Supplementary file 1. Furthermore, E.J.v.Z. and M.v.d.L searched trials registers on 13 March 2018 with the terms 'rosacea' and 'rhinophyma': metaRegister of Controlled Trials ([www.controlled-trials.com](http://www.controlled-trials.com)), U.S. National Institutes of Health Ongoing Trials Register ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)), Australian and New Zealand

Clinical Trials Registry ([www.anzctr.org.au](http://www.anzctr.org.au)), World Health Organization International Clinical Trials Registry platform ([www.who.int/trialsearch](http://www.who.int/trialsearch)), the Ongoing Skin Trials Register ([www.nottingham.ac.uk/ongoingskintrials](http://www.nottingham.ac.uk/ongoingskintrials)). Two authors (E.J.v.Z., Z.F.) examined the bibliographies of included and excluded studies for further potentially eligible studies. We did not apply language restrictions and several articles were translated. Two authors independently assessed the titles and abstracts from the searches (E.J.v.Z., Z.F.). The same two authors independently assessed the obtained full-text papers of all potentially eligible included studies. Disagreements were resolved through discussion.

### **Data extraction and risk of bias assessment**

Study details and outcome data were collected independently by two authors (E.J.v.Z. and Z.F.) using a piloted data extraction form. Disagreements on data entry were resolved through discussion. The following details were extracted: design, year of publication, setting, country of origin, number, gender and age of participants, ocular involvement, drop-outs and losses to follow-up, intervention, outcomes, baseline data, funding and conflict of interest. Two authors (E.J.v.Z., Z.F.) independently assessed risk of bias using the Cochrane Collaboration's domain-based assessment tool.<sup>12</sup>

### **Statistical analysis**

We calculated risk ratios (RR) for dichotomous outcomes and mean differences (MD) for continuous outcomes and their associated 95% confidence interval. When RRs were statistically significant, we calculated number needed to treat for one additional beneficial outcome (NNTB) or number needed to treat for one additional harmful outcome (NNTH). In the absence of substantial heterogeneity ( $I^2$  statistic < 60%), data reported for our outcomes were pooled using a random effects model, and summarised with the  $I^2$  statistic. All analyses were undertaken using RevMan 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark).

### **Certainty of evidence**

We applied GRADE to assess the certainty of evidence for the prespecified outcomes of the main comparisons using GRADEproGDT (<http://grade.pro.org>) to generate Summary of Findings Tables (see Supplementary file 1 for details on Methods, Results and 25 Summary of Findings Tables).<sup>13</sup> See Table 1 for GRADE Working Group grades of evidence.

## **RESULTS**

### **Search results**

The updated searches identified an additional 219 citations. Trial register searching revealed 38 ongoing studies, totalling 257 references. Fourteen duplicates, and 160 references were excluded after examination of titles and abstracts. The remaining 83 studies were assessed for eligibility and only 46 were included.<sup>14-57</sup> See Figure 1.

## Description of the studies

One hundred fifty-two studies were included (eight references report on two studies),<sup>14-158</sup> comprising 20,944 participants (mean age 48.6 years). More women (12,575) than men (5313) were included; in 3056 the gender was unreported. Study sample sizes varied from 6 to 1299 participants, but most were between 30 and 100. The trials were grouped into 12 categories of interventions: topical brimonidine; topical oxymetazoline; topical metronidazole; topical azelaic acid; topical ivermectin; topical metronidazole, azelaic acid and/or other topical treatments in different treatment arms; oral antibiotics; oral antibiotics combined with topical treatments; oral antibiotics compared with topical treatments; other systemic treatments; laser and light-based therapies; and other treatments or combined treatments.

Full details of all included and excluded studies (starting from the original 2004 review) are in Supplementary file 1, sections Characteristics of included studies and Characteristics of excluded studies.

## Risk of bias in included studies

Only 16/152 studies were at low risk of bias<sup>28,33,51,87,93,135,138-140,147,150,155</sup>, 52 were assessed as high risk of bias and the remaining 84 studies as at unclear risk of bias. See Figure 2.

## Evidence based treatments

Of the 152 studies, 34 provided no usable or retrievable data that could contribute to the results (see Table 6 in Supplementary file 1).<sup>46-79</sup> Important reasons were that none of our outcomes were addressed, no separate data for rosacea, or limited data reported in conference abstracts. The remaining 118 studies covered 93 comparisons.

We have summarized pivotal study results in a phenotype-led approach to provide guidance for clinical decision making as well as guideline development. Details and results on all 152 studies are reported in Supplementary file 1.

### Treatment of transient erythema and flushing

No RCTs were available.

### Treatment of persistent erythema

Brimonidine and oxymetazoline are topical  $\alpha$ -adrenergic agonists which induce transient vasoconstriction of cutaneous superficial blood vessels resulting in reduction of facial erythema after application.<sup>15,30,138,139</sup> Both reduce erythema within 30 minutes, reaching a peak between three to six hours, after which the effect diminishes and erythema returns to baseline.



### *Brimonidine*

Two studies (low risk of bias) showed, after three hours, a 2 grade improvement in Patient's Self Assessment of erythema (PSA, 0 to 4, clear to severe) in 114/277 using topical brimonidine 3 mg/g gel versus 54/276 using vehicle (RR 2.11, 95% CI 1.60 to 2.78;  $P < 0.001$ ;  $I^2 = 0\%$ ; NNTB 5, 95% CI 3 to 7; high certainty evidence).<sup>139</sup> In the brimonidine group adverse events were reported in 88/277 participants compared to 68/276 in the vehicle group (RR 1.29, 95% CI 0.98 to 1.69;  $I^2 = 0\%$ ; moderate certainty evidence). In both studies, adverse events were mild and transient. Most frequently reported were worsening of erythema, flushing, pruritus and skin irritation. During the four week follow-up, no rebound erythema was observed. Physicians' assessments were in accord with patients' assessments (high certainty evidence).

### *Oxymetazoline*

In two studies (unclear risk of bias) participants' assessments using the Subjective Self-Assessment (SSA, 0=no signs of unwanted redness, 4=severe redness) showed 2 grade improvement after three hours in 99/446 treated with oxymetazoline 1% cream and in 59/439 treated with vehicle (RR 1.65, 95% CI 1.23 to 2.21;  $P < 0.001$ ;  $I^2 = 0\%$ ; NNTB = 11, 95% CI 7 to 27; moderate certainty evidence).<sup>15,30</sup> In the oxymetazoline group 94 adverse events were reported in 446 participants versus 70 in 439 participants in the vehicle group (RR 1.32, 95% CI 0.97 to 1.78;  $I^2 = 13\%$ ; moderate certainty evidence). Application site dermatitis, pruritus, and erythema, worsening of inflammatory lesions and headache were the most reported adverse events and were considered mild or moderate in severity. During the 29 days follow-up period six patients in the oxymetazoline group experienced rebound erythema versus two in the vehicle group. Physicians' assessments were in accord with patients' assessments (moderate certainty evidence).

### Treatment of telangiectasia

#### *Laser and other light-based therapies*

Although widely used for reducing erythema and telangiectasia, only a few small sample size RCTs (16 to 49 patients) provided data on laser and light-based therapies (predominantly low certainty evidence for various outcomes). There was low to moderate certainty evidence that (long) PDL, Nd:YAG laser and intense pulsed light therapy reduce erythema and especially telangiectasia.<sup>131,151</sup> This was supported by several other studies.<sup>40,100,110,144</sup>

### Treatment of papules/pustules

#### *Topical azelaic acid*

Azelaic acid is available as 15% gel, 20% cream and 15% foam. Seven studies at unclear risk of bias evaluated azelaic acid twice daily versus vehicle.<sup>20,35,86,90,123,137</sup> Quality of life was addressed in two<sup>19,136</sup>, but with no to little differences between groups at the end of the study (high certainty evidence). In six studies, participants-assessed improvement (marked or excellent) was reached in 648/1132 with azelaic acid versus 439/1091 with vehicle (RR 1.40, 95% CI 1.28 to 1.53;  $P < 0.001$ ;  $I^2 = 0\%$ ; NNTB = 6, 95% CI 5 to 8).<sup>20,35,86,123,137</sup> These results were comparable with physicians' assessments, both high certainty evidence. There was little to no difference in number of participants experiencing an adverse event: 200/799 on azelaic acid versus 143/760 with vehicle (four studies, RR 1.29, 95% CI 0.92 to 1.81;  $I^2 = 46\%$ ; moderate certainty evidence).<sup>20,35,86,137</sup> Adverse events were transient, mild to moderate intensity, with burning, stinging or irritation most commonly reported. In three studies the lesion count reduction was 10-11 lesions with vehicle indicating a treatment effect, but the mean difference (MD) favoured azelaic acid (-3.00 lesions, 95% CI -4.13 to -1.86;  $P < 0.001$ ;  $I^2 = 9\%$ ; high certainty evidence).<sup>20,35,137</sup> Azelaic acid reduced erythema slightly (physician-assessed, high certainty evidence).<sup>35,86,90,123,137</sup>

#### *Topical ivermectin*

Two studies at low risk of bias compared topical ivermectin 1% cream once daily with vehicle.<sup>155</sup> More participants in the ivermectin group (467/910) experienced improvements in quality of life than in the vehicle groups (153/461), and at end of the study patients considered rosacea had "no [negative] effect on their overall quality of life" (RR 1.55, 95% CI 1.34 to 1.79;  $P < 0.001$ ;  $I^2 = 0\%$ ; NNTB = 6, 95% CI 4 to 8; high certainty evidence). Good to excellent improvement was reported by 615/910 participants with ivermectin compared to 169/461 with vehicle (RR 1.84, 95% CI 1.62 to 2.09;  $P < 0.001$ ;  $I^2 = 0\%$ ; NNTB = 3, 95% CI 3 to 4; high certainty evidence) and physicians' assessments were in concordance (moderate certainty evidence). There was no difference in the number of participants experiencing an adverse event (62/1050 with ivermectin versus 45/567 with vehicle, RR 0.83, 95% CI 0.54 to 1.28;  $I^2 = 26\%$ ; moderate certainty evidence).<sup>24,155</sup> With ivermectin skin burning, pruritus and dry skin were more frequently reported. Reductions in lesion counts (three studies) were between 20 and 27 with ivermectin and 12 to 23 with vehicle, with a MD between groups of -8.09 lesions (95% CI -9.82 to -6.35;  $P < 0.001$ ;  $I^2 = 52\%$ ; high certainty evidence), again showing treatment effect of the vehicle.<sup>24,155</sup>

#### *Topical metronidazole*

Topical metronidazole is available as 0.75% gel and 1% cream. Nine trials at low to high risk of bias compared metronidazole versus placebo.<sup>82-85,87,88,91,103,111</sup> Data from three studies could not be pooled for participants' assessments due to substantial heterogeneity (65%) but indicated

metronidazole was more effective than placebo (low certainty evidence), which was in line with physicians' assessments of 94/195 improving with metronidazole and 40/139 with placebo (RR 1.98, 95% CI 1.29 to 3.02;  $P = 0.002$ ;  $I^2 = 44\%$ ; moderate certainty evidence).<sup>85,88,111</sup> Data from six studies showed that 379/1375 participants reported an adverse event with metronidazole compared to 64/398 with placebo (RR 1.19, 95% CI 0.94 to 1.51;  $I^2 = 0\%$ ; moderate certainty evidence).<sup>83-85,88,103,111</sup> Adverse events were mild, consisted of pruritus, skin irritation, and dry skin. No SDs were provided for lesion counts and erythema, data were skewed but appeared to support those reported as physician-assessed improvement (both moderate certainty evidence).

#### *Topical azelaic acid versus topical metronidazole*

Three studies at unclear risk of bias (total 451 participants) reported contradictory data for this comparison (moderate certainty evidence).<sup>97,105,130</sup> Azelaic acid might be slightly more beneficial when compared to metronidazole (according to participants and physicians) but the difference may not be important. Azelaic acid likely results in a small and possibly unimportant increase in adverse events when compared with topical metronidazole. Reductions in lesion counts were comparable in both groups.

#### *Topical ivermectin versus topical metronidazole*

Topical ivermectin 1% cream once daily likely improved quality of life slightly more than topical metronidazole 0.75% twice daily, based on one study in 962 patients at low risk of bias (RR 1.11, 95% CI 1.01 to 1.21;  $P = 0.02$ ; NNTB = 15, 95% CI 8 to 100; moderate certainty evidence).<sup>156</sup> Reduction in DLQI was 5.18 in the topical ivermectin group and 3.92 in the topical metronidazole group (both meeting minimal important difference (MID)).<sup>159,160</sup> Good to excellent improvement based on participant's assessments was reported by 409/478 with ivermectin versus 362/484 with metronidazole (RR 1.14, 95% CI 1.07 to 1.22;  $P < 0.001$ ; NNTB = 10, 95% CI 7 to 17; moderate certainty evidence).<sup>156</sup> There was no difference in number of participants reporting an adverse event. Physicians' assessments in two studies were in concordance with participants' assessments.<sup>20,155</sup> Reduction in lesion counts was 27.70 (SD 8.85) with ivermectin compared to 23.60 (SD 8.23) with metronidazole (MD -4.10, 95% CI -5.18 to -3.02;  $P < 0.001$ ; high certainty evidence).<sup>156</sup>

#### *Minocycline foam*

Minocycline foam (1.5%, 3% versus vehicle) was evaluated in a 12 week study including 232 participants at low risk of bias.<sup>33</sup> Reductions in overall RosaQoL score was 0.4 with minocycline versus 0.2 with vehicle. The investigators report " $P = 0.003$ ", but as RosaQoL MID has not been established, data are difficult to interpret. Mean lesion count reduction was 21.1 (SD 8.1) with minocycline versus 7.8 (SD 8.0) with vehicle (MD -13.30, 95% CI -15.82 to -10.78). Investigator's

Global Assessment supported these results. In the minocycline foam group 46/79 reported an adverse event versus 31/78 with vehicle (RR 1.47, 95% CI 1.05 to 2.04; P = 0.02; NNTH = 5, 95% CI 3 to 32). Minocycline related adverse events were eczema, burning sensation or worsening rosacea. There was moderate certainty evidence for all outcomes.

#### *Clindamycin cream or gel*

Two studies at unclear risk of bias (629 participants) indicated clindamycin 1% cream or gel twice daily was not more effective than vehicle for any of the outcomes (low to moderate certainty evidence).<sup>32</sup>

#### *Clindamycin combined with tretinoin gel*

One study at low risk of bias with 87 participants evaluated the combination of clindamycin phosphate 1.2% with tretinoin 0.025% in a gel versus placebo.<sup>135</sup> No differences between groups were seen for quality of life, physician assessments, erythema, and lesion counts, but there were more adverse events in the active treatment group such as dry skin, scaling and worsening of rosacea. Moderate certainty evidence for all outcomes.

#### *Remaining topical treatments*

Studies evaluating permethrin, dapson, sodium sulphacetamide with sulphur, pimecrolimus and some more unusual treatments (e.g. tranexamic acid, P-3075 cream, SEI003 cream, praziquantel ointment, diclofenac sodium gel, incobotulinumtoxinA injections, kanuka honey) were at unclear to high risk of bias, inadequately reported or provided very limited data, but are addressed in Supplementary file 1.

#### *Oral tetracyclines*

Two short studies (four and six weeks) including a total of 151 participants, at unclear risk of bias, compared oral tetracycline 250 mg twice daily with placebo.<sup>106,121</sup> The certainty of evidence was low for all outcomes. Tetracycline may result in a large reduction in lesion count, which is supported by physician-assessed improvement in rosacea severity. However, patients considered there was no difference in effectiveness between tetracycline and placebo.<sup>106</sup>

Two studies at low risk of bias<sup>93</sup> and two studies at unclear risk of bias<sup>19,34</sup> assessed doxycycline 40 mg versus placebo. None assessed participant-assessed rosacea severity. There was high certainty evidence that more participants with doxycycline 40 mg reached IGA clear or almost clear (91/353) than with placebo (53/354) (RR 1.69, 95% CI 1.26 to 2.28; P < 0.001;  $I^2 = 0\%$ ; NNTB = 9, 95% CI 6 to 20).<sup>19,93</sup> One study was excluded from pooling ( $I^2 = 70\%$ ) due to lower number of lesions at baseline.<sup>19</sup> The MD of pooled data was -5.51 lesions (95% CI -7.81 to -3.21; P < 0.001;  $I^2 = 0\%$ ;

moderate certainty evidence).<sup>93</sup> Doxycycline 40 mg probably reduced erythema slightly based on three studies and assessed with CEA (MD -0.48 (95% CI -0.97 to 0.00; P = 0.05;  $I^2$  = 28%; moderate certainty evidence).<sup>19,93</sup> Slightly more adverse events occurred with doxycycline 40 mg (RR 1.27, 95% CI 1.08 to 1.49; moderate certainty evidence) but the majority was considered mild or moderate in both groups.<sup>19,34,93</sup>

Low certainty evidence from one study (91 participants) at unclear risk of bias showed that 40 mg doxycycline is at least as effective as 100 mg, with fewer side effects.<sup>94</sup>

A non-inferiority study of minocycline 100 mg with doxycycline 40 mg was assessed as at unclear risk of bias.<sup>43</sup> Patients' assessments showed that 22/40 participants with minocycline achieved excellent or good improvement compared with 20/40 in the doxycycline 40 mg group (RR 1.10, 95% CI 0.72 to 1.67; low certainty evidence). These findings were in accordance with lesion count reductions.

Quality of life was assessed using RosaQoL and the MD was -0.24 (95% CI -0.30 to -0.18; P < 0.001; low certainty evidence), a small and possibly unimportant difference favouring minocycline.

Physicians' assessments based on IGA (clear or near clear) favoured minocycline (RR 3.43, 95% CI 1.67 to 7.04; P < 0.001; NNTB = 2, 95% CI 2 to 4; high certainty evidence). There was no difference in number of patients experiencing an adverse event (RR 1.17, 95% CI 0.83 to 1.65; low certainty evidence) with the adverse events being similar (e.g. gastro-intestinal side effects and headache).

In one study (unclear risk of bias) with 60 participants, minocycline 45 mg with or without topical azelaic acid demonstrated similar effectiveness in reducing inflammatory lesions 2013)(low certainty of the evidence).<sup>142</sup> There was a reduction of 11 to 12 lesions in both treatment arms.

#### *Azithromycin versus doxycycline*

Azithromycin 500 mg three times a week (and then tapered) versus doxycycline 100 mg daily was evaluated in one study at high risk of bias (67 participants).<sup>80</sup> There were no differences in effectiveness and safety for any of the outcomes (very low certainty evidence). Both treatments reduced inflammatory lesions by 16 to 18 lesions within three months.

#### *Isotretinoin versus placebo*

Low dose isotretinoin 0.25 mg/kg was compared to placebo over four months in difficult to treat 'papulopustular' rosacea (cycline-refractory or frequently relapsing) in a study at unclear risk of bias.<sup>39</sup> After four months, participants assessed satisfaction on a VAS rated from 0 to 100 (higher being better) showed median values of 80 in the isotretinoin group versus 9 in the placebo group (low certainty evidence). Isotretinoin likely improves quality of life as measured with the Skindex (moderate certainty evidence) with scores showing median relative variations of -49.4% in the isotretinoin-treated group (108 participants) compared with -18.0% in the placebo group (48

participants)(investigators reported "P = 0.002"). Sixty-two of 108 (57.4%) treated with isotretinoin reached 90% reduction in inflammatory lesion count versus 5/48 (10.4%) in the placebo group RR 5.51 (95% CI 2.37 to 12.83; P < 0.001; NNTB = 2, 95% CI 2 to 3; high certainty evidence). The median reduction in lesion count was 13 lesions (92% reduction) in the isotretinoin-treated group and 6 lesions in the placebo group (36%). This was supported by the physicians' assessments. Treatment related adverse events were more frequently reported in the group treated with isotretinoin (75/108 (69.4%)) than with placebo (21/48 (43.4%))(RR 1.59, 95% CI 1.12 to 2.24; P = 0.009; NNTH = 4, 95% CI 2 to 11; moderate certainty evidence). Eczema, cheilitis, dry skin, abdominal pain, myalgias/arthralgias and dry eyes, which are well known side effects of isotretinoin, were reported in the active treatment group.

#### *Isotretinoin versus doxycycline*

One study at low risk of bias examined low dose isotretinoin 0.3 mg/kg versus doxycycline 100 mg for 14 days and then tapered to 50 mg.<sup>140</sup> A small difference in favour of isotretinoin was observed in participants' assessments (total of 261 participants) of good to excellent improvements (RR 1.23, 95% CI 1.05 to 1.43; P = 0.009; NNTB 7, 95% CI 4 to 25), in lesion count reduction (MD -3, 95% CI -5.18 to -0.82; P = 0.007) and physicians' assessments of marked improvement or complete remission (RR 1.18, 95% CI 1.03 to 1.36; P = 0.02; NNTB = 9, 95% CI 5 to 50). There was no difference in number of patients (299 in total) experiencing an adverse event (RR 1.19, 95% CI 0.74 to 1.92). Certainty of evidence was moderate for these outcomes. There was high certainty evidence of no difference in improvement of erythema or telangiectasia.

#### *Remaining systemic treatments*

Results on other systemic treatments are discussed in Supplementary file 1.

#### Treatment for phyma

Surgical therapies including ablative laser therapies have been used with reportedly good results for clinically noninflamed phyma, but no eligible RCTs were identified. For clinically inflamed phymas both doxycycline and isotretinoin are recommended, but no supporting evidence based on RCTs is available.<sup>8</sup>

#### Treatment for ocular features

One study with 37 patients (unclear risk of bias) showed that ciclosporin ophthalmic emulsion 0.05% twice daily improved quality of life compared to artificial tears as assessed with the Ocular Surface Index (OSDI) (scale 0 to 100, 100 = worst).<sup>119</sup> MD after three months was -8.6 (95% CI -15.42 to -1.78; P = 0.01). The physicians used the Schirmer's test which demonstrated a MD of 4.1 mm (95% CI 1.66 to 6.54; P = 0.001), confirming improved tear production, and increased tear break-up time (TBUT)

(MD 3.6 seconds, 95% CI 2.59 to 4.61;  $P < 0.001$ ). There was no difference in number of participants with an adverse event. Low certainty evidence for all outcomes.

Ciclosporin ophthalmic emulsion twice daily was compared with doxycycline 100 mg twice daily for the first month followed by two months once daily in a study at high risk of bias (38 participants).<sup>14</sup> Quality of life assessed with the OSDI was MD -8.81, 95% CI -14.32 to -3.32;  $P = 0.002$  favouring ciclosporin ophthalmic emulsion. This was confirmed by patients' assessments based on a symptom score (0 to 9, higher = worse) with a MD of -1.85 (95% CI -2.60 to -1.10;  $P < 0.001$ ). The Schirmer's test (MD 2.11 mm, 95% CI 0.82 to 3.40;  $P = 0.001$ ), TBUT (MD 2.32, 95% CI 0.81 to 3.83;  $P = 0.003$ ), the eyelid score and the cornea/conjunctival sign score all favoured ciclosporin ophthalmic emulsion. Low certainty evidence for all outcomes.

One study at unclear risk of bias (130 participants) evaluated omega 3 fatty acids (180 mg eicosapentaenoic acid and 120 mg docosahexaenoic acid) one capsule twice daily versus placebo twice daily for dry eyes in rosacea.<sup>16</sup> Moderate certainty evidence for all outcomes. Participants used the Dry Eye questionnaire and Scoring System (DESS) to evaluate this outcome (0–6 mild, 6.1–12 moderate, 12.1–18 severely symptomatic dry eye). The mean change from baseline was -5.30 (SD 1.52) in the 65 participants treated with omega 3 fatty acids compared with -0.20 (SD 1.59) in the 65 participants treated with placebo (MD -5.10, 95% CI -5.63 to -4.57;  $P < 0.001$ ). MD of the Schirmer's test (MD 1.70 mm, 95% CI 0.62 to 2.78;  $P = 0.002$ ), TBUT (MD 3.30 seconds, 95% CI 2.86 to 3.74;  $P < 0.001$ ) and Meibom gland score (lower score is better)(MD -1.28, 95% CI -1.53 to -1.03;  $P < 0.001$ ) all favoured omega 3 fatty acids.

### Combination of treatments

One study (unclear risk of bias) with 190 patients examined the combination of brimonidine 0.33% gel in the morning with ivermectin 1% cream in the evening (to address both persistent erythema and papules/pustules) versus vehicles.<sup>42</sup> According to participants' assessments (good or excellent)(RR 1.42, 95% CI 1.12 to 1.80;  $P = 0.004$ ; NNTB = 4, 95% CI 3 to 13) and the physician's global assessment (clear or almost clear)(RR 1.66, 95% CI 1.18 to 2.35;  $P = 0.004$ ; NNTB = 4, 95% CI 2 to 13), combined treatment was effective in treating both features, with reported reductions of erythema (RR 1.84, 1.38 to 2.46;  $P < 0.0001$ ; NNTB = 3, 95% CI 2 to 5) and papules/pustules. The percentage reduction from baseline was 78.3% for the active treatment group versus 65.5% for the vehicles group.

One study assessed at unclear risk of bias in 72 participants that examined combining doxycycline 40 mg with topical metronidazole versus metronidazole alone was not specifically designed to treat

more than one feature (focussing on papules/pustules rather than on erythema).<sup>98</sup> The results of this study indicated that combining treatments had a beneficial effect on more than one feature.

### Maintenance treatments

Three RCTs addressed the effectiveness of combined maintenance treatments following disease control. Topical metronidazole 0.75%, ivermectin 1% and azelaic acid 15% gel seemed effective and safe for maintenance therapy.<sup>41,91</sup>

## **DISCUSSION**

This updated review including 152 studies focuses on studies and comparisons that were likely to provide evidence-based and reliable treatment options, within a phenotype approach.

For transient reduction of persistent erythema, there is high certainty evidence to support the efficacy and safety of brimonidine gel and moderate certainty evidence for oxymetazoline cream over 12 hours after application. Both topical treatments probably result in little to no difference in number of participants experiencing an adverse event when compared with vehicle (moderate certainty evidence).

For persistent erythema and telangiectasia, there was low to moderate certainty evidence of the efficacy of (long) pulsed dye laser, Nd:YAG laser and intense pulsed light therapy.

For papules/pustules of rosacea, there is high certainty evidence that topical azelaic acid and topical ivermectin reduce lesion counts, and moderate certainty evidence for topical metronidazole and topical minocycline. It still needs to be established whether topical azelaic acid is more effective than topical metronidazole, but topical ivermectin appeared slightly more effective than topical metronidazole (moderate certainty evidence).

As for systemic treatments of papules/pustules, there is low certainty evidence that tetracycline is effective and moderate certainty evidence for doxycycline (40 mg). There is low certainty evidence that 40 mg doxycycline is at least as effective as 100 mg, with fewer adverse events with 40 mg. The evidence for the efficacy and safety of low dose minocycline 45 mg is of low certainty and of very low certainty for azithromycin. There is probably little to no difference between minocycline 100 mg and doxycycline 40 mg (moderate certainty evidence). Serious adverse events have been reported in rare cases with minocycline like autoimmune hepatitis, lupus erythematosus and hyperpigmentation of the skin and tissues.<sup>4</sup> Low dose isotretinoin 0.25 mg/kg results in far more participants with minimum 90% lesion count reduction when compared with placebo (high certainty evidence). Isotretinoin is known to be teratogenic and should therefore not be prescribed to pregnant women



or women that are trying to become pregnant.<sup>4</sup> Compared to doxycycline (100 mg tapered to 50 mg after two weeks), low dose isotretinoin 0.3 mg/kg probably results in a small effect, but that difference in reducing lesion counts may not be important. Both oral isotretinoin and oral doxycycline showed important reductions in lesion counts (moderate certainty evidence).

For most treatments, or combinations thereof, there is no clear evidence favouring any with regard to higher remission rates or fewer adverse events. However, more participants experienced an adverse event with topical azelaic acid, topical minocycline and oral isotretinoin, when compared with vehicle or placebo.

No studies could be included that addressed treatment of phymatous rosacea.

For ocular rosacea, ciclosporin 0.05% ophthalmic emulsion was shown to be more beneficial than artificial tears (low certainty evidence). Ciclosporin 0.05% was also more effective than doxycycline 200 mg for the first month and 100 mg for the following two months for all the addressed outcomes (low certainty evidence). Omega 3 fatty acids improved symptoms of dry eyes and improved tear gland function (moderate certainty evidence).

### Combination of treatments

One study demonstrated that combination of brimonidine gel in the morning and ivermectin cream in the evening was effective in treating both erythema and papules/pustules compared with vehicles.<sup>42</sup>

### Maintenance treatments

Topical metronidazole 0.75%, ivermectin 1% and azelaic acid 15% gel seem effective and safe as a maintenance treatment regarding papules/pustules. Other maintenance treatments for rosacea have not been addressed in RCTs.

### *Agreements and disagreements with other studies or reviews*

Since the last update of this review in 2015,<sup>161</sup> a number of other reviews or guidelines have been published.<sup>162-166</sup> The Canadian Clinical Practice guidelines for rosacea, published in 2016, used the 2015 version of this review as a source of clinical evidence and basis for making recommendations using the GRADE approach.<sup>162</sup>

A Swiss S1 guideline for the treatment of rosacea has been published in which assessments of evidence (A-E) were used, and 13 national experts on rosacea reached consensus on recommendations.<sup>163</sup> They concluded that there was level A evidence (no major design flaws and at least one double-blind RCT) for pimecrolimus, topical retinoids, topical permethrin, topical benzoyl peroxide/clindamycin, topical erythromycin and topical dapsone, oral zinc sulphate and oral ampicillin, on which we clearly disagree. There were no details on inclusion criteria for studies, neither basis of appraisal of quality nor judgements on the risk of bias. No patients or patient advocacy groups were included and the guideline appeared solely reliant on the contribution of expert panels. In contrast, and in terms of recognising the significant impact of this condition on patients, we have tried to ensure that we received timely, patient-relevant input at all stages of conducting and reporting this review and have included two patients as co-authors. Furthermore, we applied the widely adopted GRADE approach to rate the certainty of evidence for our predefined outcomes of the most clinically relevant comparisons.

The global ROSacea COnsensus panel (ROSCO), an international panel of dermatologists and ophthalmologists developed recommendations for diagnosis, classification and treating rosacea, on a phenotype rather than subtype approach.<sup>6,8</sup> The classification recommendations from that consensus were adopted in this update.

Three reviews on topical ivermectin in rosacea have been published.<sup>164-166</sup> One was a narrative review describing the pharmacological properties of ivermectin and available data on efficacy and tolerability.<sup>164</sup> Another was a systematic review with clinical guideline recommendations in which the Jadad score (randomisation, double blinding and dropouts) was used to assess risk of bias but not a key criterion (concealment of treatment allocation).<sup>165</sup> Nevertheless, their conclusions are in concordance with those in this review. As head-to-head studies comparing various topical treatments are generally lacking, a network meta-analysis comparing the efficacy, safety and tolerability of topical ivermectin with other currently available topical agents has been conducted.<sup>166</sup> This study "expanded and built upon" earlier versions of our review<sup>161,167</sup> and was conducted and reported robustly. The authors concluded that topical ivermectin appeared to be more effective than other topical treatment options for papules/pustules of rosacea, with similar safety and tolerability.

Limitations of our review were that the lack of response from investigators regarding missing trial details largely resulted in less favourable risk of bias assessments (unclear as opposed to low risk). Unfortunately, our outcomes time until improvement and duration of remission were not or minimally addressed in the studies. The lack of standardised and validated scales was challenging for pooling data. Scales should be developed with greater focus on specific features rather than

conflation of multiple features into a single scale as previously done with the subtype approach. This focus will provide greater clarity on the effect of interventions on distinct rosacea features. As an example, this would avoid the current conundrum of extracting the effect on persistent erythema versus perilesional erythema of inflammatory lesions in studies on "papulopustular rosacea".

In conclusion, we have summarized the data and most pivotal comparisons of RCTs for rosacea in a phenotype-led approach providing certainty of evidence for predefined outcomes. Supplementary file 1 is the complete and latest updated version of the systematic review "Interventions for rosacea", which includes all 93 comparisons, including 25 Summary of findings tables. This review can therefore be the basis for developing or updating evidence-based guidelines and for guidance in clinical decision making.

### Acknowledgements

The authors would like to thank the librarian Jan Schoones, Walaeus Library of Leiden University Medical Centre for his help with the searches for trials.

We would like to thank Na Luo, from the Department of Dermatology Southwest Hospital Army Medical University Chongqing, China and Xiamomeng Liu, Department of Dermatology, Flevo Hospital Almere, the Netherlands for her translation of Zhang from Chinese into English.<sup>43</sup>

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Table 1 GRADE Working Group grades of evidence

**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect

**Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

**Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

**Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnote: <http://gradeepro.org>